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Introduction to Epidemiology

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KEY CONCEPTS

1. *Epidemiology is the study of the distribution and determinants of diseases within human populations. Research in this field is based primarily upon observing people directly in their natural environments.*
2. *Epidemiology can be used for descriptive purposes, such as surveillance of the occurrence (incidence) of a particular illness.*
3. *Epidemiology can be used for analytic purposes, such as studying risk factors for disease development.*
4. *Epidemiologic methods can be used to assess the performance of diagnostic tests.*
5. *Epidemiology can be used to study the progression or natural history of a disease.*
6. *Epidemiologic methods can be used to study prognostic factors, which are determinants of the progression of a disease.*
7. *Epidemiology can be used to evaluate treatments for a disease.*

PATIENT PROFILE

A 29-year-old previously healthy man was referred to the University of California at Los Angeles (UCLA) Medical Center with a history of fever, fatigue, lymph node enlargement, and weight loss of almost 25 lb over the preceding 8 months. He had a temperature of 39.5°C, appeared physically wasted, and had swollen lymph nodes. Laboratory evaluation revealed a depressed level of peripheral blood lymphocytes. The patient suffered from simultaneous infections involving Candida albicans *in his upper digestive tract, cytomegalovirus in his urinary tract, and* Pneumocystis carinii *in his lungs. Although antibiotic therapy was administered, the patient remained severely ill.*

INTRODUCTION

Epidemiology is a fundamental medical science that focuses on the distribution and determinants of disease frequency in human populations. Specifically, epidemiologists examine patterns of illness in the population and then try to determine why certain groups or individuals develop a particular disease whereas others do not.

Knowledge about who is likely to develop a particular disease and under what circumstances they are likely to develop it is central to the daily practice of medicine and to efforts to improve the health of the public. To prevent an illness, health care providers must be able both to identify persons who because of personal characteristics or their environment are at high risk, and to intervene to reduce that risk. This type of knowledge emerges in many cases from epidemiologic research.

This book serves as an introduction to epidemiologic methods and the ways in which these methods can

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be used to answer key medical and public health questions. This chapter begins by considering a particular disease, as described in the Patient Profile. Focusing attention on one disease enables us to demonstrate the important contribution of epidemiology to current knowledge about this condition. Although the emphasis is on a single disease, it should be recognized that epidemiologic methods can be applied to a wide spectrum of conditions, ranging from acute illnesses, such as outbreaks of food-borne infections, to long-term debilitating conditions, such as Alzheimer's disease.

The man in the Patient Profile was referred to the UCLA Medical Center in June 1981. At the time, there was no obvious explanation as to why a healthy young man would suddenly develop concurrent infections in three different organ systems involving three different microorganisms. More surprising was the nature of the infections that were present. Opportunistic infections, such as those caused by the parasite *P carinii,* are infectious illnesses that tend to occur only in persons with lowered resistance, such as that which results from impaired immune responses. However, the young man described in the Patient Profile did not have any obvious underlying causes of immune dysfunction. For example, he did not have cancer or severe malnutrition and he did not use immunosuppressants. Why then was his body overwhelmed by the infections? This question was given a heightened sense of urgency by the severity of the patient's illness.

This patient was not the first to be referred to the UCLA Medical Center with this clinical presentation. Within the preceding 6 months three other previously healthy young men with recent histories of weight loss, fever, and lymph node enlargement had been examined. All had *P carinii* pneumonia and *C albicans* infections.

Why were four patients with similar symptoms appearing at about the same time in the same location? Suspecting that the illnesses in these four patients might be related, the UCLA physicians notified public health officials and prepared a descriptive report of their findings for publication.

Was this new appearance of a rare and life-threatening form of pneumonia confined to the UCLA Medical Center, or was it being observed by physicians elsewhere? If the experience at UCLA was unique, the entire episode might be regarded as a medical curiosity—unusual, but not a reason for great public health concern. On the other hand, if patients similar to those at UCLA were appearing in clinics or medical offices elsewhere, this episode could not be so easily dismissed. Within a matter of weeks, public health authorities received reports of outbreaks of *P carinii* pneumonia among previously healthy young men in San Francisco and New York City.

In the United States, the federal agency that is responsible for monitoring unusual patterns of disease occurrence is the Centers for Disease Control and Prevention (CDC). Recognizing the potential for the widespread emergence of this new, unexplained, and debilitating condition, the CDC established a special task force to collect more detailed information on the affected persons. In addition, the CDC issued a formal request to report such patients to all state health departments. Between June and November 1981, 76 instances of *P carinii* pneumonia were identified in persons who did not have known predisposing illnesses and were not taking immunosuppressants. A few months later, the disease that afflicted these patients was named the acquired immune deficiency syndrome (AIDS).

PERSON, PLACE, & TIME

The physicians at UCLA played a crucial role in establishing the presence of a new disease in their community. The first few affected patients identified with any outbreak of disease are referred to as **sentinel cases.** The story of the first few AIDS patients is particularly dramatic because of the severity of the illness and the extent and speed with which the disease spread to others. A sudden and great increase in the occurrence of a disease within a population is referred to as an **epidemic.** It quickly became apparent, however, that the emergence of AIDS was not confined to a few communities. A rapidly emerging outbreak of disease that affects a wide range of geographically distributed populations is described as a **pandemic.** In 1981, no one could have predicted that through 2002 almost 900,000 persons in the United States would be diagnosed with AIDS and over 500,000 deaths from AIDS would be reported nationally. By 1996, AIDS was the eighth most common cause of death in the United States and the third most common cause of death for persons between the ages of 25 and 44 years. With the introduction of effective combination drug therapy, the death rate from AIDS has declined in the United States and in other industrialized nations. In developing nations a much more devastating picture is emerging; for instance, of the estimated 3,000,000 deaths annually from AIDS worldwide, about three-fourths occur in sub-Saharan Africa.

Looking back to 1981, when AIDS had not yet been recognized as a clinical entity, it is instructive to consider the features of the sentinel cases that suggested a possible connection. All the patients with AIDS who presented to the UCLA clinicians suffered from the same rare opportunistic infections. Had the infections involved more conventional human pathogens—or less

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severe symptoms—the entire episode might have gone unnoticed for some time.

Beyond their clinical similarities, the sentinel cases shared other features as summarized in Table 1–1. All four patients were previously healthy homosexual men in their early 30s (personal characteristics) who resided in Los Angeles (place) and first became ill in the 9 months ending in June 1981 (time). These three dimensions—**person, place,** and **time**—are the features traditionally used to characterize patterns of disease occurrence, as discussed in Chapter 3.

THE EPIDEMIOLOGIC APPROACH

Epidemiology is the study of the distribution and determinants of disease frequency in human populations. Interest in frequency or occurrence of disease derives largely from a basic tenet of epidemiology, namely that disease does not develop at random. In essence, all persons are not equally likely to develop a particular disease. The level of risk for different individuals typically is a function of their personal characteristics and environment.

As applied to the outbreak of AIDS, for instance, it is highly unlikely that of the first four cases seen in Los Angeles all would have occurred in homosexual males if the disease was striking at random. The repeated occurrence of AIDS in homosexual men suggested that this segment of the population had an increased risk of developing the disease. Other high-risk groups for AIDS, including hemophiliacs and injecting drug users, were soon identified. On the surface, these three groups seemed to have little in common. On closer examination, however, it became evident that an increased risk of exposure to the blood of other persons was the factor they all shared.

Contemporary medical research is devoted largely to investigating the biologic elements of disease development. For example, in the study of AIDS, a microbiologist tends to focus on the infectious agent, the human immunodeficiency virus (HIV). An immunologist might concentrate on the primary target of HIV infection, the $CD4^+$ T lymphocyte, which coordinates a number of immune functions. The epidemiologist, on the other hand, views a disease from both a biologic and a social perspective. It is not enough to know that HIV is transmitted primarily through contaminated blood. The epidemiologist must be able to understand the circumstances of HIV transmission among humans. Here, the influence of social factors is undeniable. The spread of AIDS in human populations cannot be fully appreciated without recognizing the role of certain behaviors, such as sexual practices or injecting drug use.

The desire to study social factors that impinge on health has definite implications for how epidemiologic research is conducted. In most instances, this research involves observations of phenomena that occur naturally within human populations. Such an approach is unique among the medical sciences. Two features distinguish the epidemiologic approach from other biomedical sciences: (1) the focus on human populations and (2) a heavy reliance on nonexperimental observations.

At first, the focus on human populations may not seem distinctive. Ultimately, all medical research is motivated by a desire to prevent or control human illnesses. However, the process leading to that goal may take various routes. Laboratory scientists, for example, often rely on experiments that involve nonhuman animals, cells in tissue culture, or biochemical assays. Although these studies offer important advantages to the investigator, such as precise control over the experimental conditions, certain limitations must also be recognized. Obviously, a laboratory environment may not accurately reflect the actual conditions of exposure in the external world. Of equal importance is the recognition that animals of different species may have dissimilar responses to experimental manipulations. It cannot be assumed that biologic effects detected in rodents, for instance, will necessarily apply to humans.

Epidemiologists avoid these concerns by attempting to study people directly in their natural environments. With this approach, it is not necessary to make assumptions about similarity of effects either across species or across doses and routes of exposure. The epidemiologist actually observes the patterns of exposure and disease development as they naturally occur within human populations. Without such information, it would not be possible to reach a definitive conclusion about the extent of disease related to a particular agent.

As with any scientific method, the epidemiologic approach has inherent constraints. In observational research, which comprises much of epidemiology, the investigator merely watches the phenomena under study (ie, the epidemiologist has no control over the events

Table 1–1. Characteristics of sentinel cases of AIDS in Los Angeles,1981.

Characteristics of Sentinel Cases	Personal Attributes
Age	Early 30s
Gender	Male
Prior health	Good
Sexual preference	Homosexual
Place of occurrence	Los Angeles
Time of occurrence	October 19, 1980 to June 19, 1981

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that occur). It is often difficult, therefore, to separate the causal contributions of the exposure of interest from the causal contributions of other background influences in the population. Even direct measurement of the degree of exposure may not be possible in some settings, thereby forcing the epidemiologist to rely on indirect estimates.

The epidemiologist's perspective of the relationship between exposure to risk factors and the development of disease in human populations may appear rather crude in comparison to exacting research performed at the molecular level. Indeed, epidemiology is not particularly useful for characterizing the precise biologic mechanisms of disease development. The epidemiologist frequently sees only how different levels of exposure across groups of the population affect the comparative likelihood that those groups will develop disease. Typically, the epidemiologist can identify the personal, social, and environmental circumstances under which a disease tends to occur, without being able to explain the exact processes that give rise to the disease.

Medical progress often is best advanced when the sciences that focus on subcellular and molecular basic research work in tandem with the population-oriented science of epidemiology. For example, as bench scientists were struggling to characterize the molecular properties of HIV, epidemiologists already determined that AIDS is a contagious disease that is spread through certain interpersonal behaviors. As the painstaking search continues for improved treatment, or even a cure or vaccine, public health professionals have recommended measures to prevent the spread of HIV by reducing the frequency of high-risk practices, such as casual, unprotected sex and sharing needles among injecting drug users.

THE APPLICATIONS OF EPIDEMIOLOGY

Epidemiologic methods can be used for a number of distinct purposes. In the following sections, these areas of application are specified, with corresponding illustrations drawn from the literature on AIDS.

Disease Surveillance

Perhaps the most basic question that can be asked about a disease is "What is the frequency with which the disease occurs?" To answer this question, it is necessary to know the number of persons who acquire the disease (cases) over a specified period of time, and the size of the unaffected population. Measures of frequency of occurrence of a disease, described in Chapter 2, are used to characterize the patterns of the occurrence of the disease, described in Chapter 3, and the medical surveillance of the disease, discussed in Chapter 4. Typically, the criteria used to define the occurrence of a disease depend on current knowledge about the disease; such criteria may become more refined as the causes of a disease are delineated and new diagnostic tests are introduced. For example, in 1982, the CDC created an initial, relatively simple surveillance definition for AIDS: "A disease, at least moderately indicative of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease."

A more specific definition became possible once the causative agent, HIV, was identified and tests for the detection of antibodies to the virus were developed. In 1987, the CDC surveillance definition was expanded to incorporate clinical conditions that are indicative of AIDS. A 1993 revision further expanded the surveillance definition to include three additional indicator conditions (pulmonary tuberculosis, recurrent pneumonia, or invasive cervical cancer), or the presence of a severely depressed $CD4^+$ T-lymphocyte count. In 2000, the CDC integrated monitoring of both HIV infection and AIDS.

Such changes in diagnostic criteria can have a profound effect on the apparent frequency of a disease. The expanded definition of AIDS introduced in 1987 led to an increase in the number of reported AIDS patients by about 50% during the next 2 years. The 1993 revision more than doubled the number of persons who met the surveillance definition. Most of the latter increase was attributable to persons made eligible on the basis of reduced $CD4^+$ T-lymphocyte counts and HIV infection. Accordingly, analysis of trends in disease occurrence over time must account for the possible effects of any temporal changes in diagnostic criteria.

The identification of patients with a disease can occur through various mechanisms, most commonly by physician and laboratory reporting. In the United States, a number of diseases, including AIDS, must be reported to public health authorities. Monitoring the patterns of occurrence of a disease within a population is referred to as **surveillance.** There are many potential benefits from the collection of surveillance data. This type of information (1) can help to identify the new outbreak of an illness, such as AIDS, (2) can provide clues, by considering the population groups that are most affected by the illness, to possible causes of the condition, (3) can be used to suggest strategies to control or prevent the spread of disease, (4) can be used to measure the impact of disease prevention and control efforts, and finally, (5) can provide information on the burden of illness, data that are necessary for determining health and medical service needs.

The course of the AIDS pandemic in the United States is depicted in Figure 1–1. To diminish the im-

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Figure 1–1. The number of cases of AIDS diagnosed in the United States using the 1993 CDC surveillance definition, after adjustments for reporting delays, 1985–2002. (Modified and reproduced from CDC: HIV/AIDS Surveillance Report 2002;**14**:1.)

pact of changes of the surveillance definition over time, a single definition, the 1993 CDC version, was used throughout. From 1985 through 1992 there was an unrelenting rise in the number of newly reported cases. From 1993 through 1998 there was a progressive fall in the number of newly reported cases. Between 1999 and 2001 the level of AIDS cases was unchanged, with a slight increase in 2002. It should be noted that the information in Figure 1–1 relates to the **number** of newly diagnosed cases per year. Changes in the counts of new cases can be affected by a number of factors, including among others, changes in the following:

1. Frequency with which the disease occurs
2. Definition of the disease
3. Size of the population from which the cases develop
4. Completeness of the reporting of the cases.

With respect to point 2, the same surveillance definition was used consistently for all years in Figure 1–1, minimizing any confounding influence of a change in definition of the disease over time. With regard to point 3, growth in the size of the population of the United States could not explain more than a trivial amount of the rise in the cases seen between 1985 and 1992. The national population grew at only about 1% per year, whereas the average annual increase in reported persons with AIDS exceeded 30%. Moreover, the declines in AIDS cases observed between 1993 and 1998 occurred while the population of the United States continued to grow. Concerning point 4, the overall completeness of reporting of AIDS cases is estimated to be about 85% in the United States. Although there is some internal variation by geographic subregion and patient population, it is unlikely that these patterns could have given rise to more than a small part of the trend observed in Figure 1–1. Since items 2 through 4 do not appear to account for the marked changes in the annual numbers of reported AIDS cases, it is reasonable to conclude that the observed trends reflect true changes in the occurrence of the disease.

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For surveillance purposes, the size of the source population from which cases arise usually is estimated from census data. The frequency of disease occurrence is then expressed as the number of new cases developing within a specified time among a standard number of unaffected individuals. For example, during 2002 over 42,000 cases of AIDS were reported in the United States; the U.S. population in 2002 was about 288,000,000. Dividing the number of reported cases by the size of the population yields 0.00015 cases per person during that year. For ease and consistency of expression of such figures, epidemiologists typically express such frequencies of disease occurrence for a population of a specified size, say 100,000 persons. By multiplying 0.00015 by 100,000, the number 15 is obtained. That is to say, within a standard population of 100,000 persons in the United States, 15 persons would have been reported as developing AIDS during 2002. This measure of the rapidity of disease occurrence is referred to as an **incidence rate.** More information on incidence rates is presented in Chapter 2.

To characterize patterns of disease occurrence, incidence rates may be determined for groups defined by geographic area. For example, Figure 1–2 in annual incidence rates for AIDS are presented by place of residence in the United States. During 1997, the incidence rate for the District of Columbia was the highest observed, with 162.4 reported cases for every 100,000 residents. At the other extreme, North Dakota experienced the lowest annual incidence rate (0.5 cases per 100,000 residents). In other words, AIDS occurred in the District of Columbia about 325 times (162.4/0.5 = 325) more frequently than in North Dakota. Why are persons in the District of Columbia so frequently diagnosed with AIDS; conversely, why are persons in North Dakota so infrequently affected?

Answers to such questions typically do not derive from surveillance information alone. Surveillance data usually are limited to general characteristics of affected persons, such as their age, race, sex, and place of residence. Although variations in incidence rates according to these demographic features can lead to the identifica-

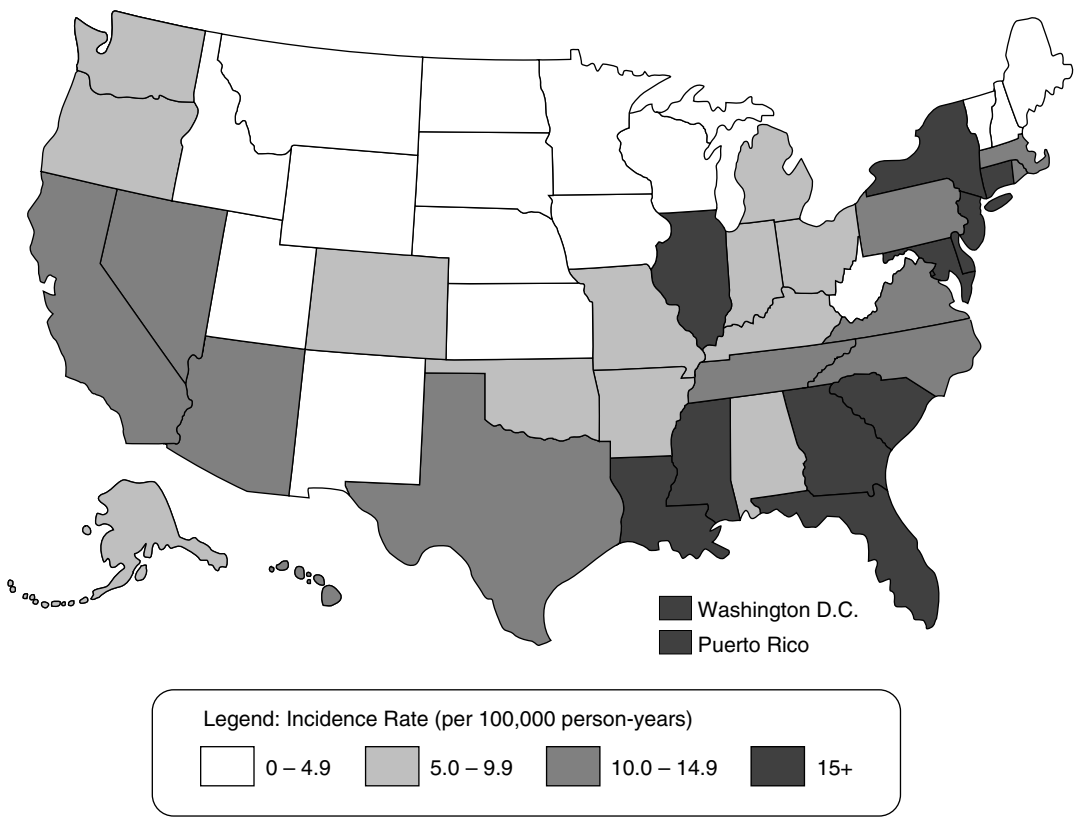

Figure 1–2. The incidence rates of AIDS per 100,000 person-years in the United States, 2002. (Modified and reproduced from CDC: HIV/AIDS Surveillance Report 2002;**14**:27–28.)

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tion of high-risk groups, explanations for these patterns generally require more in-depth investigation into personal characteristics, behaviors, and environments.

Searching for Causes

To study personal and environmental characteristics, epidemiologists often rely on interviews, review of records, and laboratory examinations. Through such sources of information, a profile of characteristics that accompany the disease can be generated. Associations between these characteristics and the occurrence of disease can arise by coincidence, by noncausal linkages to other features, or by cause-and-effect relationships.

The epidemiologist is primarily interested in the last category, ie, determinants of disease development, also known as **risk factors.** Identification of risk factors can provide a better understanding of the pathways leading to disease acquisition, and consequently, better strategies for prevention.

Again, returning to the AIDS example, early epidemiologic studies played an important role in determining the cause of this disease. Within the first 5 months after recognition of this syndrome, the CDC had received reports on 70 patients with AIDS in four urban centers. Of these individuals, 50 homosexual male patients with AIDS were interviewed; also interviewed were 120 unaffected homosexual male comparison subjects. Persons who are affected with a disease are referred to by epidemiologists as **cases,** and unaffected comparison persons are called **controls.** Comparison of the responses from cases and controls revealed that the AIDS patients had a higher number of sexual partners. This type of investigation is referred to as a **case–control study;** the basic design of such a study is illustrated in Figure 1–3.

In essence, this study is an attempt to look backward in time to identify characteristics that may have contributed to the development of the disease. The increased number of sexual partners—as well as a greater frequency of syphilis among cases—suggested that AIDS resulted from a sexually transmitted infectious agent, later discovered to be the HIV virus. Case–control studies are described in Chapter 9.

Comparison of historical exposures reported by cases and controls can provide suggestive evidence of a cause-and-effect relationship. This type of information, however, may be distorted or **biased** by the fact that the ability of cases and controls to recall earlier exposures differs. Such bias could be avoided by using a **cohort study** design, in which exposure is assessed among unaffected persons, and subjects are then observed for sub-

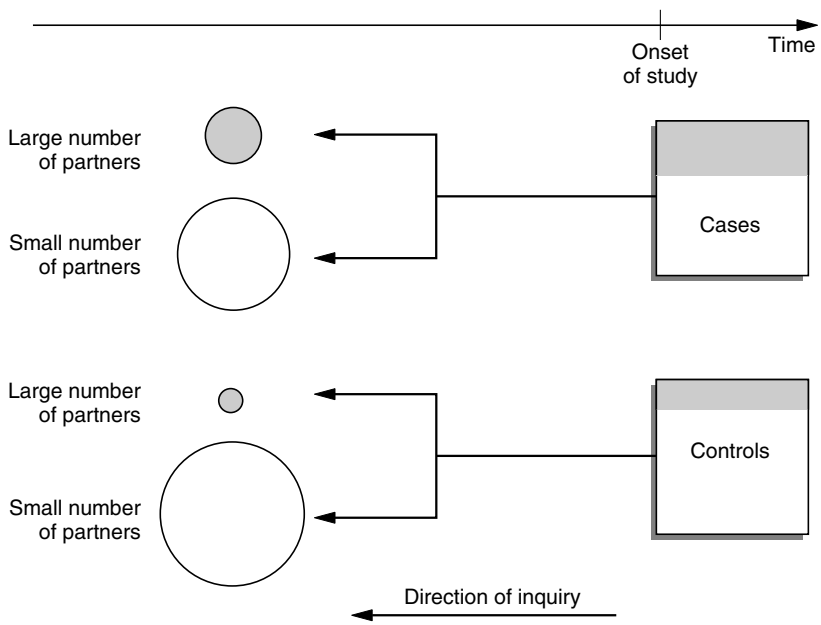

Figure 1–3. Schematic diagram of a case–control study of the association between the number of male sexual partners of homosexual men and the risk of AIDS. Shaded areas represent subjects with a large number of sexual partners, and unshaded areas represent subjects with a small number of sexual partners.

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sequent development of illness. To collect such data, a cohort of 2507 homosexual men without antibodies to HIV (seronegative) was questioned about their sexual practices, and then followed for development of antibodies to HIV (seroconversion). Within 6 months, 95 men (3.8%) seroconverted, and the likelihood or **risk** of developing HIV antibodies was found to be related to receptive anal intercourse. The basic design of this cohort study is illustrated schematically in Figure 1–4. Cohort studies are discussed in Chapter 8.

The proportion of new AIDS cases related to sexual transmission between homosexual men has declined over time in the United States. In 2002, slightly more than half of all reported AIDS cases occurred among men who have sex with men. Use of injected drugs accounted for almost one-fourth of cases, and heterosexual contact was responsible for almost one-sixth of all cases. The diminished role of homosexual contact as a contributing factor in the occurrence of AIDS in the United States reflected avoidance of high-risk behaviors, although there is evidence that high-risk behaviors continue in some communities.

HIV transmission through heterosexual intercourse continues to increase in the United States and is the leading mode of transmission worldwide. The practice of safe sex can prevent the transmission of AIDS among heterosexuals, as demonstrated clearly in a cohort study by de Vincenzi (1994). That European study included heterosexual couples in which only one partner was HIV seropositive at the outset. Couples were followed for an average of almost 2 years to determine the relationship between certain sexual practices and the risk of HIV transmission to the uninfected partner. Condom use was found to be an effective barrier to HIV transmission. Among 124 couples who consistently used condoms there were no episodes of seroconversion of uninfected partners. However, among 121 couples whose condom use was inconsistent, there were 12 instances of seroconversions of initially uninfected partners.

Diagnostic Testing

The purpose of diagnostic testing is to obtain objective evidence of the presence or absence of a particular condition. This evidence can be obtained to detect disease at its earliest stages among asymptomatic persons in the general population, a process referred to as **screening.** In other circumstances, diagnostic tests are used to confirm a diagnosis among persons with existing signs or symptoms of illness. Ideally, a diagnostic test would correctly distin-

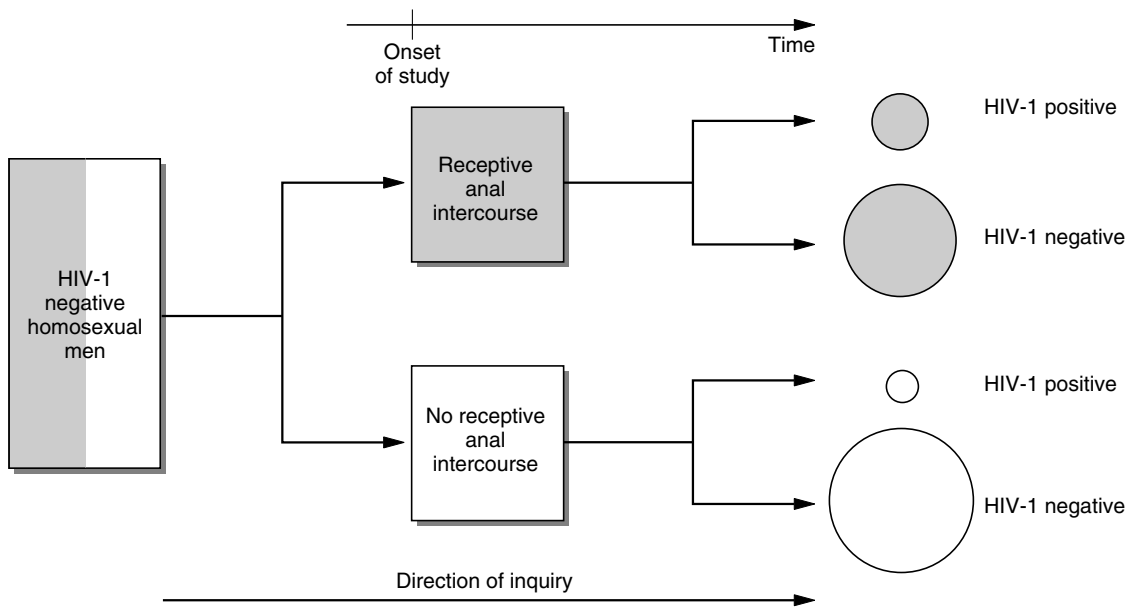

Figure 1–4. Schematic diagram of a cohort study of the association between receptive anal intercourse and risk of being HIV positive. Shaded areas indicate subjects who practice receptive anal intercourse, and unshaded areas represent subjects who do not.

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guish affected persons from unaffected persons; unfortunately, as is true of most diagnostic tests, assays for HIV infection are not perfect.

Occasionally, a positive test result will incorrectly suggest that infection is present in an unaffected person. This type of outcome is referred to as a **false positive,** because the positive test result was in error. Obviously, a false-positive finding for HIV infection could be devastating to the tested individual, so every effort must be made to keep such errors to a minimum. A test with a very low percentage of false-positive results is said to have **high specificity** (Figure 1–5).

Another type of error occurs when a test incorrectly suggests that infection is not present (negative test result) in an affected person. This type of outcome is referred to as a **false negative,** because the negative test result was in error. A false-negative finding for HIV infection could provide inappropriate reassurance to an infected person, thereby delaying the start of treatment and possibly increasing the risk of spread to other persons. A test with a very low percentage of false-negative results is described as having **high sensitivity** (Figure 1–6). More detail on measures of test accuracy is presented in Chapter 6.

A number of different tests for the presence of HIV infection are available. The screening approach used most widely is to attempt to detect antibodies to the virus. This strategy is based on two assumptions: (1) HIV-infected persons have detectable antibodies, and (2) persons with detectable antibodies to the virus are infected with HIV. In practice, these assumptions appear to be reasonably valid among patients beyond the first few months of infection. The time required to mount an antibody response sufficient for detection (seroconversion) varies across patients, but the vast majority seroconvert in less than 6 months following initial HIV infection.

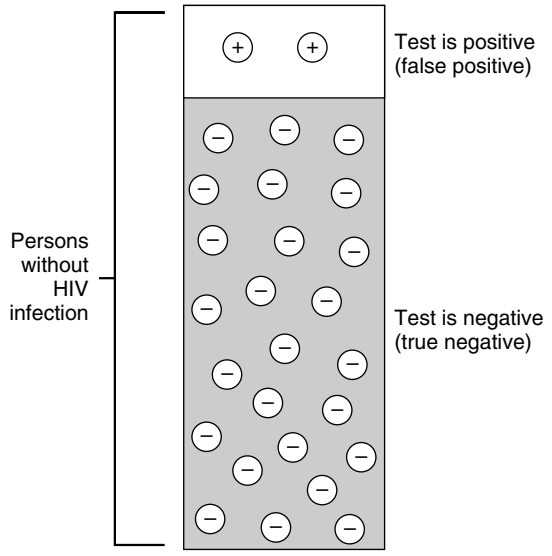

Figure 1–5. When a diagnostic test is applied to persons without HIV infection, it is highly specific if the true negative test results (shaded area) greatly outnumber erroneous positive test results (unshaded area).

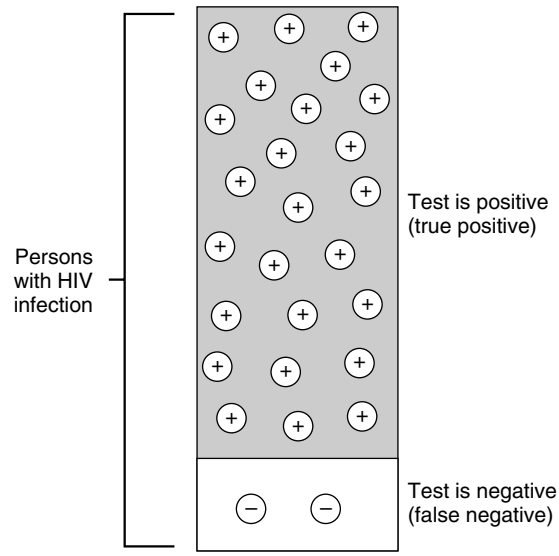

Figure 1–6. When a diagnostic test is applied to persons with HIV infection, it is highly sensitive if the true positive test results (shaded area) greatly outnumber the erroneous negative test results (unshaded area).

The performance of an enzyme-linked immunosorbent assay (ELISA) test for antibodies to HIV was first reported in 1985. Among 74 patients who met the CDC clinical surveillance definition for AIDS and had unequivocal ELISA test results, 72 (97%) had detectable antibodies. In other words, a false-negative outcome was observed for only 2 patients (3%). Among 261 healthy blood donors with unequivocal ELISA test results, 257 (98%) had no detectable antibodies (ie, a false-positive outcome was found for 4 persons [2%]). Thus, the ELISA test was judged to be both sensitive and specific, and it has become the most widely employed screening test for HIV infection.

A number of different ELISA kits are commercially available. When false-negative ELISA results occur among high-risk individuals, the most likely explanation is that the test was performed prior to the development of detectable antibody levels in the immediate postinfection period. False-positive ELISA test results have been observed among patients with medical con-

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ditions unrelated to HIV, such as autoimmune disorders, hematologic malignancies, and infections with viruses other than HIV, among patients recently vaccinated against hepatitis B or influenza, and among patients who have received immune globulin. Technical or human errors in performing the ELISA test also can produce false-positive results.

Considering the potential for error, it is recommended that a positive ELISA test be repeated in duplicate. If either of the follow-up tests is positive, a supplementary test should be performed. The most widely used confirmatory test is the Western blot. This type of test is not recommended for screening purposes, because Western blot can produce a substantial proportion of equivocal results among persons who are negative to all other HIV tests.

The presence of infection with HIV also can be detected through other approaches, such as the detection of viral genetic material in plasma.

Determining the Natural History

After being informed of a new diagnosis, patients most frequently ask "What will happen to me?" This question cannot be answered with absolute certainty because of variations in outcome across individual patients. Usually the best guidance for predictions is the experience of other patients who are similar to the patient in question. Even when the ultimate outcome can be predicted with some confidence, the actual sequence of events can vary widely among patients.

Consider, for example, a patient newly diagnosed as being HIV positive. In this instance, with the advent of new treatments it is reasonable to question whether the full syndrome of AIDS will develop, and if it does how long it will take to occur. In attempting to address these questions, the physician might consult published research on the progression of HIV-related illness. Usually these data are collected on large groups of patients. By noting the timing of critical events for each patient (eg, date of determination of HIV infection, development of clinical symptoms of illness, demonstrable changes in immune function, diagnosis of AIDS, and subsequent clinical events), the progression of the disease can be divided into phases.

5 When these events are summarized for many patients, precise and accurate estimates of the typical sequence of events—the **natural history** of the illness—can be constructed. Some authors restrict the use of the descriptor "natural" to situations in which medical treatment is unavailable or ineffective. Others use the term more broadly, to indicate the typical course of an illness, regardless of whether it can be treated effectively.

There are several ways to characterize the natural history of an illness. One straightforward measure is the **case fatality,** which represents the percentage of patients with a disease who die within a specified observation period. For example, among the 11,740 reported adolescent and adult patients diagnosed with AIDS in 1985 in the United States, 10,946 are known to have died before 1998. In other words, the case fatality was

$$\frac{10{,}946}{11{,}740} \times 100\% = 93.2\%$$

The approach to determining the case fatality is illustrated schematically in Figure 1–7.

Another method of characterizing the natural history of a disease is to estimate the typical duration from diagnosis to death (**survival time**). As an illustration, a study was conducted in a rural part of Uganda, a country with a high prevalence of HIV infection. In this setting, in which economic and other conditions limited treatment to simple and affordable drugs, the natural history of HIV infection was characterized. The study involved persons who were seropositive for HIV and a comparison group of seronegative individuals. All subjects were identified in 1990 and were evaluated clinically every 3 months until death or the end of calendar year 1995, whichever came first. For the initial 3 years after seroconversion, there was no difference in survival between the HIV-positive persons and the persons without infection. However, by 5 years following seroconversion only 83% of the HIV-positive persons were still alive, compared with 94% of the seronegative persons.

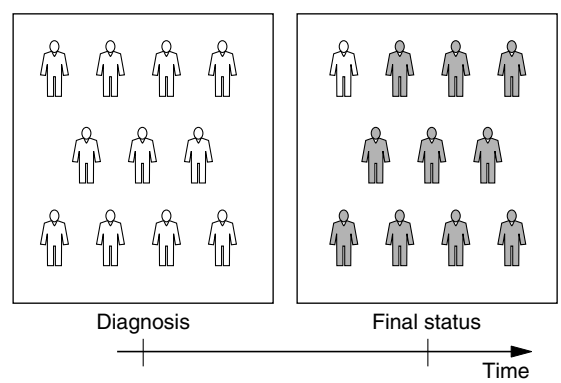

Figure 1–7. Schematic diagram of the concept of case fatality. Shaded figures represent patients who are deceased and unshaded figures represent patients who are alive.

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A number of factors can affect the apparent natural history of HIV-related illnesses. HIV infection may exist for a prolonged period of time prior to the development of symptoms that lead to a clinical diagnosis of AIDS. Recognition of the presence of infection during this preclinical phase clearly depends on the availability of an effective screening test, the sensitivity of the test to detect early infection, and the extent to which the screening test is applied in the population. The expectation, therefore, is that in the earliest years of the AIDS epidemic, prior to the development and widespread application of screening tests for HIV, the diagnosis was made at comparatively advanced stages of infection, when symptoms already were evident.

Comparisons of the survival experience of patients with AIDS both regionally and internationally also might be distorted by differences in the extent to which screening for HIV and $CD4^+$ T-lymphocyte counts are employed in the different locations.

Changes over time in the criteria used to diagnose AIDS could also alter the apparent survival experience of patients with this disease. For example, analysis of patients with HIV registered in Italy between July 1987 and December 1991 revealed that when the 1987 CDC case definition for AIDS was applied, half of the patients survived for 24 months more or longer. The length of survival that is met or exceeded by 50% of the study population is referred to as the **median survival time.** When the broadened 1993 CDC case definition was retrospectively applied to this same population, not only did a larger number of patients meet the definition, but the median survival time was found to exceed 57 months. In other words, the population of patients who met the 1993 case definition tended to have a more favorable outcome than the subset that met the earlier definition.

In estimating the natural history of HIV infection, an increasingly important issue is the impact of more effective treatments on the progression of illness. The benefits of improved clinical treatment are not confined to persons in advanced stages of disease. As shown schematically in Figure 1–8, the introduction of effective therapy can delay the onset of AIDS after infection with HIV, as well as extend the duration of survival after a diagnosis of AIDS. Several studies in industrialized countries have demonstrated that the rate of progression from HIV infection to a diagnosis of AIDS was reduced by about 75% after the introduction of highly active antiretroviral therapy (HAART). Similarly, the rate of progression from AIDS to death declined by about two-thirds after the introduction of HAART.

Searching for Prognostic Factors

Analysis of survival can be employed to identify groups of patients with unusually favorable (or unfavorable) clinical outcomes. Characteristics that relate to the likelihood of survival are referred

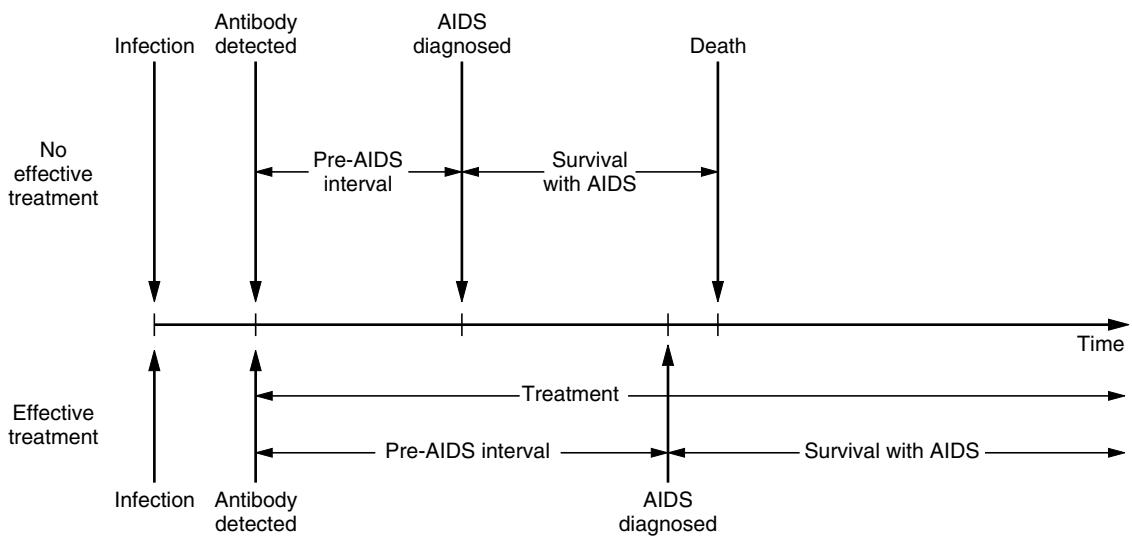

Figure 1–8. Comparison of the clinical progression of HIV infection prior to effective treatment and after the introduction of effective treatment. Aggressive early treatment delays the onset of AIDS and prolongs survival after the diagnosis of AIDS.

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to as **prognostic factors.** The approach to identifying prognostic factors can be illustrated by a study conducted by Mellors and colleagues (1997). Using data collected from the Multicenter AIDS Cohort Study of homosexual men in the United States, the investigators evaluated factors related to the progression from initial infection with HIV to two clinical end points: (1) the development of AIDS and (2) AIDS-related death. A total of 1604 men were enrolled in the study, which included a follow-up period on average of almost 10 years. Over this time period, 998 of the participants developed AIDS and 855 died of AIDS. The design of this study is depicted schematically in Figure 1–9. Figure 1–9 shows that the study design is similar to that of the cohort study (Figure 1–4), except that the focus is on predicting survival rather than on determining risk factors for the onset of disease.

In the study by Mellors and associates, a number of potential prognostic factors were assessed, including, among others, oral candidiasis or fever, markers of immune stimulation, various lymphocyte counts including $CD4^+$ T-lymphocytes, and an assay of the plasma concentration of HIV-1 RNA (ribonucleic acid—the genetic material of the virus). The HIV-1 RNA assay provides a precise measurement of the load of the virus circulating in a patient's blood. As might be expected, some association was seen between the initial levels of the individual prognostic factors. For example, patients with higher viral loads at the start of the study were more likely to have fever or oral candidiasis and reduced levels of $CD4^+$ T-lymphocytes. Viral load also was seen as the single best predictor of the subsequent decline over time in $CD4^+$ T-lymphocyte levels, as well as in the progression to AIDS and death. Specifically, when study subjects were grouped into five ordered categories based on plasma viral load, the 6-year probability of AIDS-related death ranged from 1% among those with the lightest load, to 70% among those with the heaviest load. By combining information on HIV-1 RNA concentrations with $CD4^+$ T-lymphocyte levels, even more effective determination of the likelihood of disease progression could be made (Table 1–2).

Testing New Treatments

In the United States, all new medications must be tested and proved effective before they can be introduced into routine clinical care. The standard approach used to evaluate treatment effectiveness is the **randomized controlled clinical trial.** The term "controlled" means that patients (experimental subjects) who receive the new medication are compared with patients (control subjects) who receive either an inactive substance (placebo) or a standard treatment if one

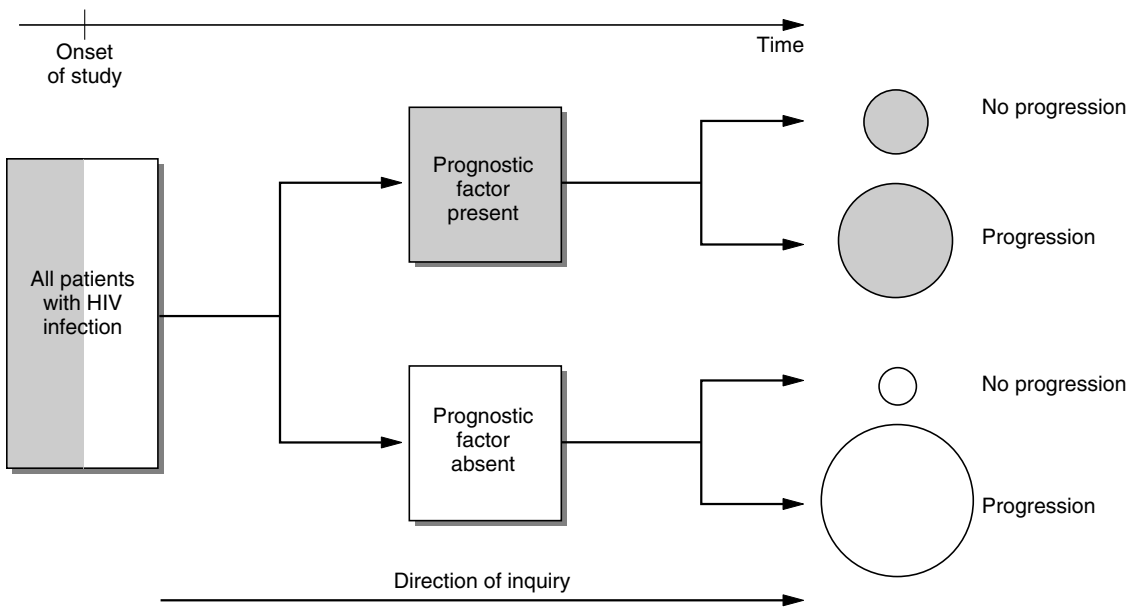

Figure 1–9. Schematic diagram of a study to evaluate prognostic factors for persons with HIV infection. The shaded areas represent patients with the favorable prognostic factor of interest and the unshaded areas represent patients without the prognostic factor of interest.

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Table 1–2. Independent prognostic factors for AIDS.

Factor	Poor Prognosis Level
Age	37 years or older
Initial presentation	Multiple diagnoses
Single diagnosis other than Kaposi's sarcoma or *P carinii* pneumonia	Thrush
$CD4^+$ T lymphocytes	Low
HIV-1 RNA level	High

exists. "Randomized" refers to a method of assignment of subjects to either the experimental or control group that is determined by chance rather than patient preference or physician selection. This type of allocation system is desirable because it tends to result in study groups that are comparable with respect to important prognostic factors. Randomized controlled clinical trials are discussed in Chapter 7.

The principles of randomized controlled clinical trials can be demonstrated by a study that has contributed to a revolution in the treatment of HIV-infected persons. That study, published by Hammer and colleagues in 1997, compared a standard therapy with a new experimental treatment regimen. The standard therapy employed two drugs (zidovudine and lamivudine), both of which are inhibitors of the HIV reverse transcriptase. By interfering with the conversion of viral genetic material to a form that can be incorporated into the host, these drugs limit the replication of HIV within host cells. The experimental treatment involved these two drugs plus another one (indinavir), which is an inhibitor of the HIV protease. Protease inhibitors interfere with the process of assembling viral components after replication of HIV genetic material. The experimental therapy, therefore, involved a simultaneous attack on two separate and distinct steps in the process of HIV reproduction. Prior studies had demonstrated that this combined therapy was capable of reducing viral plasma load and raising $CD4^+$ T-lymphocyte levels. Since favorable responses were seen in these prognostic factors, it was reasonable to anticipate that this combination therapy might diminish the rate of progression of HIV-related disease.

Hammer and colleagues undertook a randomized controlled clinical trial in which a standard two-drug reverse transciptase regimen was compared with a three-drug combined reverse transcriptase/protease inhibition experimental treatment. The basic design of the trial is depicted in Figure 1–10. Participants were recruited from 40 different clinical centers throughout the United

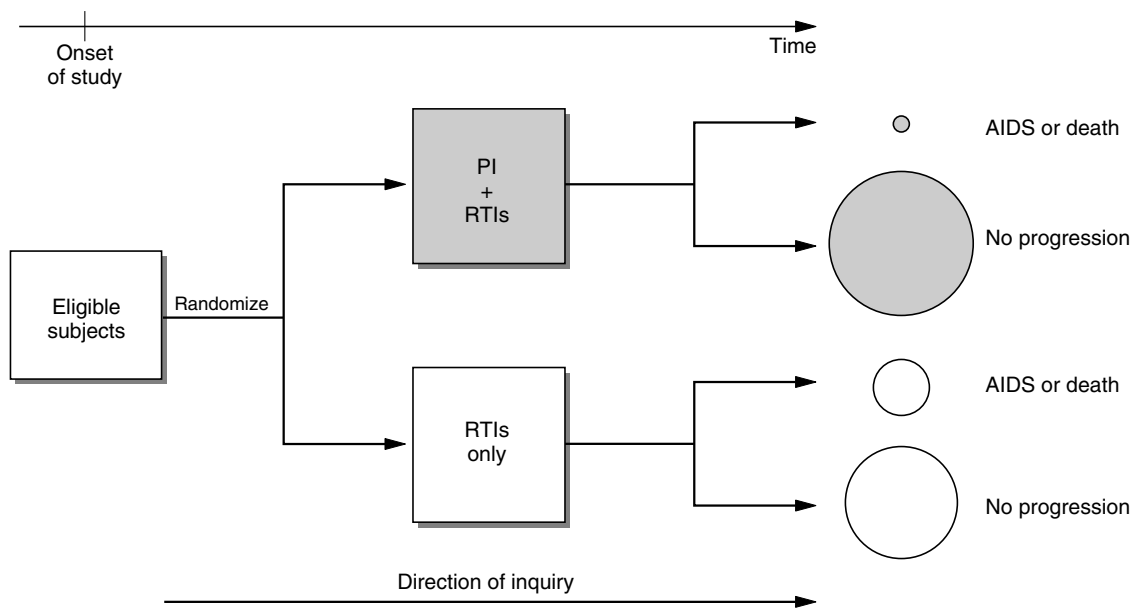

Figure 1–10. Schematic diagram of a randomized controlled clinical trial of reverse transcriptase inhibitors (RTIs), with or without a protease inhibitor (PI), for the treatment of HIV infection. The shaded area indicates patients randomized to receive combined treatment with RTIs and a PI.

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States. The subjects were required to have documentation of HIV infection and a $CD4^+$ T-lymphocyte level diminished below a predetermined level. To minimize effects of prior therapy, eligible subjects were limited to those who had not been treated previously with a protease inhibitor. A total of 1156 patients were randomized between January 1996 and January 1997, with 579 assigned to the standard therapy group and the remaining 577 assigned to the experimental therapy group. The clinical characteristics of the two groups were similar at the onset of treatment. After an average of about 38 weeks of observation, the trial was terminated because of a dramatic difference in risk of disease progression between the two groups. Within the experimental treatment group of the study, 33 patients (6%) progressed to AIDS or died. In contrast, within the standard treatment group, 63 patients (11%) progressed to AIDS or died.

The results of this trial and other similar studies clearly demonstrated the short-term therapeutic benefit of combined treatment with reverse transcriptase inhibitors and protease inhibitors. The ethical imperative to terminate this study early because of the substantial advantage of combination therapy left unresolved the question of whether this effect is sustainable over longer periods of time. Even without data on the long-term benefits, the striking results of the studies of combined reverse transcriptase and protease inhibition changed the whole approach to clinical management of HIV infection. As the search for even more effective treatments continues, randomized controlled clinical trials will serve as the definitive approach to establishing therapeutic superiority.

SUMMARY

In this chapter, we have seen how epidemiologic research has contributed to basic knowledge about AIDS:

1. The techniques of surveillance were used to determine the patterns of HIV infection and occurrence of AIDS by person, place, and time.
2. Comparisons of affected and unaffected persons led to the identification of risk factors and ultimately to the suspicion that an infectious agent was responsible for the disease.
3. Evaluation of tests for antibodies to HIV allowed improved diagnosis and prevention of spread by contaminated blood products.
4. Studies of natural history helped to define the clinical course of the illness.
5. Prognostic factors were determined through comparison of patients with favorable and unfavorable outcomes.
6. Finally, improvement in treatment was demonstrated through randomized controlled clinical trials.

The story of HIV and AIDS is particularly dramatic because it involves a devastating disease that emerged rapidly in the population and developed with minimal advance warning. It is an unfinished story because new cases are still occurring with considerable frequency, and a cure has not yet been identified. Epidemiology will continue to play an important role in monitoring progress in the prevention and treatment of HIV-related illness and AIDS.

Epidemiologic research has been pivotal in gaining insight into many different diseases. From infectious illnesses to heart disease to cancer to congenital malformations, epidemiology has provided insights into patterns of disease occurrence and underlying causal factors. Ultimately, this information can be used to help control the impact of diseases either through preventive measures or improved clinical management.

STUDY QUESTIONS

An outbreak of illness from West Nile virus (WNV) infection took place in the northeastern United States between July and October, 2001 (CDC: Serosurveys for West Nile virus infection—New York and Connecticut counties, 2000. MMWR 2001; ***50****:37.)*

Questions 1–10: For each numbered situation below, select the most appropriate term from the following lettered options. Each option can be used once, more than once, or not at all.

- ***A.*** *Epidemic*
- ***B.*** *Sentinel case*
- ***C.*** *Incidence rate*
- ***D.*** *Risk*
- ***E.*** *False-positive*
- ***F.*** *False-negative*
- ***G.*** *Risk factor*
- ***H.*** *Prognostic factor*
- ***I.*** *Natural history*
- ***J.*** *Case fatality*
- ***K.*** *Median survival*
- ***L.*** *Randomized controlled clinical trial*
- ***M.*** *Cohort study*
- ***N.*** *Case–control study*

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1. *Persons with fever/headache were ten times more likely than others to have serum evidence of WNV infection. Fever/headache is best described as*
2. *Among Staten Island residents, 2.5 per 100,000 persons developed severe WNV neurologic disease during this time period. This measure is best described as*
3. *West Nile virus had occurred for the first time in the United States the preceding year. This unusual pattern of occurrence is best described as*
4. *A person who has the symptoms consistent with severe WNV neurologic disease, but does not have definitive serologic evidence of infection*
5. *Two of 21 patients with severe WNV neurologic disease died. This is best described by*
6. *The first person with severe WNV neurologic disease became ill the week of July 15. This individual is best described as*
7. *Clinical outcome of severe WNV neurologic disease was substantially worse for elderly patients. Advanced age is best described as*
8. *A study of antiviral agents is conducted for the treatment of severe WNV neurologic disease in which treatment assignments to individual patients are made by chance*
9. *A study is conducted comparing prior use of mosquito repellent by persons with and without severe WNV neurologic disease. This is best described as*
10. *A study is conducted in which the rates of subsequent WNV infection are compared in communities with and without mosquito abatement programs. This is best described as*

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e-PIDEMIOLOGY

Overview of Epidemiology

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http://www.pitt.edu/~super1/lecture/lec7261/index.htm
http://hivinsite.ucsf.edu/InSite?page=kb-01-03

Disease Surveillance

http://www.cdc.gov/hiv/stats.htm
http://www.unaids.org/en/resources/epidemiology.asp

Searching for Causes

http://www.niaid.nih.gov/factsheets/evidhiv.htm

Diagnostic Testing

http://www.cdc.gov/mmwr/pdf/rr/rr5019.pdf

Searching for Prognostic Factors

http://hivinsite.ucsf.edu/InSite?page=kb-03-02-04#53X

Testing New Treatments

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http://www.cdc.gov/hiv/treatment.htm
http://www.pitt.edu/~super1/lecture/lec10331/index.htm

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